PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M/45016-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/001038	International filing date *(day/month/year)* 02.02.2005	Priority date *(day/month/year)* 03.02.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/366 A61K31/40 A61K31/22 A61K31/695 A61K9/20 A61P9/10		
Applicant FERRER INTERNACIONAL, S.A. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.11.2005	19.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pacreu Largo, M Telephone No. +49 89 2399-7851

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/001038

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-11	as originally filed

Claims, Numbers

24	as originally filed
1-23	received on 30.11.2005 with letter of 30.11.2005

Drawings, Sheets

1/1	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The documents cited in the International Search Report (ISR) are consecutively numbered D1-D8 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

2. Document D1 relates to pharmaceutical compositions comprising a statin. Said formulations may optionally contain an anti-foaming agent such as simethicon in an amount of about 0% to about 0.5% of the final formulation (D1, p.30, paragraph [075]). However, the only example which illustrates the addition of simethicone is example 9, which describes a pH-independent coating which comprises approximately 0.15% by weight of simethicone emulsion as dispersant. Having regard to the fact that said proportion refers to the coating only (and not to the entire formulation comprising pravasatin) and further refers to an emulsion of simethicone (and not simethicone per se), the actual proportion of simethicone in dosage forms having the coating of example 9 will be far below 0.15% by weight. Taking into account that the amount of pravasatin in said formulation is well above 5% by weight (see examples 1-5), the weight ratio of simethicone versus pravastatin is expected to be below 0.25.

   Document D2 describes the composition of commercial film-coated tablets comprising atorvastatin. Simethicone emulsion is one of a number of inactive ingredients contained in said tablets. Simethicone has the function of an auxiliary agent and therefore the weight ratio of simethicone versus atorvastatin is believed to be far below 0.25.

   Thus, the subject-matter of claims 1-23 is not novel in the sense of Art. 33(2) PCT.

3. The problem to be solved by the present invention may be regarded as the provision of an improved hypocholesterolemic composition comprising a statin which does not cause flatulence.

The solution to the problem posed is the addition of an antiflatulent agent (simethicone or dimethicone) in a weight ratio of antiflatulent agent versus statin of at least 0.25 in order to achieve an antiflatulent effect.

It is well-known that simethicone has antiflatulent effects and that it can be added to compositions comprising other active ingredients (see D4, D5). D1 explicitly points to the optional addition to compositions comprising pravastatin of anti-foaming agents such as simethicone in an amount of about 0% to about 0.5% of the final formulation (p.30, first paragraph).

The applicant states that the proportion of simethicone in D1 is too low to achieve an antiflatulent effect. However, in the absence of any evidence showing an unexpected effect in relation to the claimed weight ratio an inventive step cannot be acknowledged, Art. 33(3) PCT.

CLAIMS

1. A pharmaceutical composition comprising a statin and an antiflatulent agent wherein the weight ratio of antiflatulent agent versus statin is at least 0.25.

2. The composition of claim 1 wherein the ratio is at least 1.50.

3. The composition of any one of claims 1 and 2 wherein the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, or pharmaceutically acceptable salts and hydrates thereof.

4. The composition of claim 3 wherein the statin is simvastatin or a pharmaceutically acceptable salt thereof.

5. The composition of any one of claims 1 to 4 wherein the antiflatulent agent is selected from the group consisting of simethicone and dimethicone.

6. The composition of claim 4 wherein the antiflatulent agent is simethicone.

7. The composition of any one of claims 1 to 6 wherein the composition is a tablet, capsule, syrup, solution, powder, granule, or emulsion.

8. The composition of claim 7 wherein the tablet is a coated tablet.

9. The composition of claim 8 wherein the coated tablet comprises a core and a coating, the core comprising the statin and the antiflatulent agent.

10. The composition of any one of claims 7 and 8 wherein simvastatin is present in an amount from 2.5 to 100 mg per tablet.

11. The composition of claim 10 wherein simvastatin is present in an amount from 5 to 80 mg per tablet.

12. The composition of any one of claims 7 and 8 wherein simethicone is present in an amount from 25 to 250 mg per tablet.

13. The composition of claim 12 wherein simethicone is present in an amount of 125 mg per tablet.

14. The composition of any one of claims 1 to 13 further comprising one or more diluents, one or more binders, one or more disintegrants and one or more lubricants.

15. The composition of claim 14 wherein the diluent is selected from the group consisting of microcrystalline cellulose and their derivatives, lactose, mannitol, calcium phosphates, starch, and the mixtures thereof.

16. The composition of claim 14 wherein the binder is selected from the group consisting of starch, polyethylene glycols, polyvinylpyrrolidones, cellulose derivatives, and the mixtures thereof.

17. The composition of claim 14 wherein the disintegrant is selected from the group consisting of colloidal

silicon dioxide, croscarmellose, polyvinylpyrrolidone, starch and its pregelatinized derivatives, and the mixtures thereof.

18. The composition of claim 14 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, stearic acid, sodium stearyl fumarate, PEG 8000, and the mixtures thereof.

19. The composition of any one of claims 1 to 18 further comprising one or more antioxidants and one or more wetting agents.

20. The composition of claim 8 wherein the coating of the tablet comprises a cellulose derivative or its pharmaceutically acceptable salt, an acrylic polymer, triethyl citrate, titanium dioxide and one or more lubricants.

21. The composition of claim 17 wherein the cellulose derivative is hydroxypropyl methylcellulose.

22. The composition of any one of claims 1 to 21 further comprising one or more colouring agents.

23. A process for preparing a composition according to any one of claims 1 to 22 by direct compression of components thereof.